# Smooth Pursuit Eye Movements in Childhood-Onset Schizophrenia: Comparison with Attention-Deficit Hyperactivity Disorder and Normal Controls

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*Abnormalities of the smooth pursuit eye movements of adults with schizophrenia have been well described. We examined smooth pursuit eye movements in schizophrenic children, contrasting them with normal and attention-deficit hyperactivity disorder (ADHD) subjects, to determine whether there is continuity of eye movement dysfunction between childhood- and adult-onset forms of schizophrenia. Seventeen schizophrenic children with onset of illness by age 12, 18 ADHD children, and 22 normal children were studied while engaged in a smooth pursuit eye tracking task. Eye tracking variables were compared across the three groups. Schizophrenic children exhibited significantly greater smooth pursuit impairments than either normal or ADHD subjects. Within the schizophrenic group, there were no significant relationships between eye tracking variables and clinical variables, or ventricular/brain ratio. Childhood-onset schizophrenia is associated with a similar pattern of smooth pursuit abnormalities to that seen in later-onset schizophrenia.*


**Key Words:** eye tracking, schizophrenia, children, ADHD, saccade

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## Introduction

Since the original observation by Diefendorf and Dodge (1908) of abnormal pursuit eye movements in patients with dementia praecox, this phenomenon has been examined in numerous studies (Abel et al 1992; Clementz and Sweeney 1990; Levy et al 1993). Focusing almost exclusively upon adult populations, investigators have demonstrated that gain, defined as the ratio of eye velocity to target velocity during smooth pursuit, is reduced in schizophrenics (Abel et al 1991; Friedman et al 1995; Levin et al

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1988; Moser et al 1990; Radant and Hommer 1992; Sweeney et al 1992). In addition, the frequency of saccades during smooth pursuit is increased (Cegalis et al 1983; Friedman et al 1995; Moser et al 1990; Radant and Hommer 1992; Sweeney et al 1992) and the amount of time spent tracking the target is decreased in schizophrenia (Friedman et al 1995; Cegalis and Sweeney 1979).

More specifically, the frequency of catch-up saccades, which reposition gaze on the target when it falls behind, is increased in schizophrenics relative to controls (Friedman et al 1995; Moser et al 1990; Radant and Hommer 1992). Rates of intrusive saccades, such as anticipatory saccades, which increase the mismatch between eye position and target position, are often higher in schizophrenics relative to normals (Friedman et al 1992a; Litman et al 1994; Sweeney et al 1992), although this difference has not always reach significance (Grove et al 1991; Radant and Hommer 1992; Sweeney et al 1992, 1993).

The relationship between abnormal smooth pursuit and negative symptoms of schizophrenia has been inconsistent (Ciuffreda et al 1994; Katsanis and Iacono 1991; Sweeney et al 1992; Kelly et al 1990), and little evidence supports a relationship between acute symptom severity and smooth pursuit abnormalities (Sweeney et al 1992; Solomon et al 1987); however, abnormal neurologic signs have been found to be positively correlated with eye tracking dysfunction in adult patients (Siever and Coursey 1985; Schlenker et al 1994).

Although studies of adult schizophrenics on and off antipsychotic medication indicate that typical neuroleptics neither cause nor ameliorate smooth pursuit abnormalities (Litman et al 1989, 1994; Levy et al 1983; Spohn et al 1988; Sweeney et al 1994b), the atypical antipsychotic, clozapine, adversely affects smooth pursuit, both in terms of gain (Litman et al 1994) and in terms of catch-up saccades (Friedman et al 1992b; Litman et al 1994).

Studies of the relationship between brain morphology and eye tracking in adult schizophrenics have produced conflicting results, with some reports of a positive relationship between abnormal smooth pursuit and lateral ventricular enlargement (Weinberger and Wyatt 1982; Bartfai et al 1985), others of no significant relationship (Katsanis and Iacono 1991; Siever et al 1986; Katsanis et al 1991), and still others of a significant inverse relationship between eye tracking dysfunction and ventricular/brain ratio, measured by computerized tomography (CT) scan (Smeraldi et al 1987), and medial temporal lobe morphology, assessed with magnetic resonance imaging (MRI) (Levy et al 1992).

Most studies of eye tracking in schizophrenia have involved adult patients whose age at the onset of psychotic symptoms was typical, usually late adolescence or early adulthood. An ongoing study of 12 ambulatory adolescent schizophrenics and 12 adolescent controls, age 11–18 years, reported significantly greater catch-up saccade amplitude and a trend for lower gain in the schizophrenics (Friedman et al 1993). To the best of our knowledge, there have been no other published reports on the smooth pursuit eye movements of schizophrenic patients below the age of 18, and none on the eye movements of schizophrenics whose psychotic symptoms began in childhood.

In the present study, eye tracking was quantitatively analyzed in children, age 10–18, with childhood-onset schizophrenia and contrasted with that of age-matched normal children and children with attention-deficit hyperactivity disorder (ADHD). Smooth pursuit undergoes developmental changes up to the age of 14 (Ross et al 1993), highlighting the importance of age-matched controls in studies of eye tracking in children. In addition to determining whether continuity exists between child- and adult-onset forms of schizophrenia in terms of type and specificity of eye tracking abnormalities and clinical and neurobiological correlates, we sought to determine whether our sample of young schizophrenics would demonstrate a more severe pattern of eye tracking abnormalities than that seen in adult schizophrenics, commensurate with the greater premorbid impairment, earlier onset, and more malignant course of their illness (Alaghband-Rad et al 1995; Gordon et al 1994). Limited analysis of data from a subset of these subjects has been presented elsewhere (Gordon et al 1994).

## Methods

### *Subject*

**SCHIZOPHRENIC GROUP.** Schizophrenic subjects were participants in an ongoing study of children and adolescents with childhood-onset schizophrenia, which has been described in detail previously (Frazier et al 1994; Gordon et al 1994). Briefly, the sample consisted of 17 subjects (10 boys, 7 girls), age 10–18 (mean 14.5 ± 1.8), who met DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia, with onset of psychotic symptoms by age 12 (mean 10.1 ± 1.8). As this study involves a trial of clozapine for all participants, a history of poor response to, and/or inability to tolerate, treatment with at least two different neuroleptics was required. In fact, all study participants have been unresponsive to typical neuroleptics. Other inclusion criteria were absence of active medical or neurologic disease and premorbid full-scale IQ greater than 70. Diagnosis was determined using previous records and clinical and structured interviews of the children and parents using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age

Children—Epidemiologic Version (Orvaschell et al 1980) and of the Diagnostic Interview for Children and Adolescents—Revised (DICA-R) (Reich and Welner 1988).

Twelve schizophrenic subjects were able to perform the eye tracking task at the end of a 4-week medication washout phase, 4 subjects at the end of 6-weeks of treatment with haloperidol, and 12 subjects at the end of 6 weeks of treatment with clozapine.

**ADHD CONTROL GROUP.** Subjects with ADHD included 17 boys and 1 girl, age 9–15 (mean 12.6 ± 2.5), who were participating in a 9-week, double-blind, placebo-controlled trial of methylphenidate and dextroamphetamine described elsewhere (Elia et al 1991). All were screened for medical and neurologic disease, and all met DSM-III-R criteria for ADHD, determined via structured interviews with parent and child using the DICA-P and the DICA-C (Herjanic and Campbell 1977), and via the inclusion criteria of a score at least two standard deviations above age norms on the hyperactivity factor of the revised Conners Teacher Rating Scale (Werry et al 1975; Goyette et al 1978). ADHD subjects had been medication free a minimum of 3 days at the time eye tracking studies were performed.

**NORMAL CONTROL GROUP.** Twenty-two normal children and adolescents (16 boys, 6 girls), age 9–18 (mean 13.5 ± 2.2), were recruited through advertisements and were free of medical, neurologic, and psychiatric illness and learning disabilities as determined by history from parents, the Conners Preliminary Parent Report and the Achenbach Child Behavior Checklist (Achenbach and Edelbrock 1983) completed by parents, Conners Teacher Preliminary School Report and Conners Teacher Questionnaire (Goyette et al 1978; Werry et al 1975), physical and neurologic exam of the child, and structured interview of child and parent using the DICA-R. Any history of psychiatric illness in a first-degree relative, per parent report, was exclusionary.

Parents of all subjects provided written informed consent and subjects provided written assent for participation in the study. This study was approved by the National Institute of Mental Health (NIMH) Institutional Review Board.

### *Behavioral, Cognitive, and Neurologic Assessments*

Brief psychiatric rating scale (BPRS) (Overall and Gorham, 1962), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and Abnormal Involuntary Movement Scale (AIMS) (Rapoport et al 1985) scores were obtained on schizophrenic subjects as described previously (Frazier et al 1994), and the scores in closest temporal proximity to the dates on which eye tracking studies were performed (usually the week of testing) were used in this analysis. A detailed neurologic examination following a standardized format, which included assessment of mental status, cranial nerves, sensation, motor signs, muscle tendon reflexes, Babinski's signs, abnormal involuntary movements, coordination, gait, and primitive reflexes, was performed by a board-certified neurologist on 15 of the schizophrenic subjects near the end of the washout phase. The neurologist was not blind to diagnosis and scored neurologic signs as absent, present, or untestable.

Five schizophrenic subjects were too symptomatic during the course of this study to permit valid assessment of intelligence. With the remaining 12 subjects, IQ was measured using the Wechsler Intelligence Scale for Children—Revised (WISC-R) (Wechsler 1974). The IQ of ADHD subjects was obtained from the full WISC-R, whereas the IQ of the normal subjects was estimated using the vocabulary and block design subtests (Sattler 1992). Table 1 presents the age, gender, mean full-scale IQ, and medication status for the three groups.

Table 1. Age, Gender, Mean Full-Scale IQ, and Medication Status of Schizophrenic, ADHD, and Normal Subjects

| | Schizophrenic | ADHD | Normal |
|---|---|---|---|
| *N* | 17 | 18 | 22 |
| Age (years)[a] | | | |
| Range | 10–18 | 9–15 | 9–18 |
| Mean | 14.5 | 12.6 | 13.5 |
| SD | 1.8 | 2.5 | 2.2 |
| IQ[b] | | | |
| Range | 69–118 | 86–142 | 80–149 |
| Mean | 84.7 | 110.6 | 116.0 |
| SD | 16.8 | 16.6 | 17.9 |
| Gender | | | |
| Female | 7 | 1 | 6 |
| Male | 10 | 17 | 16 |
| Medication at testing | | | |
| Clozapine | 9 | 0 | 0 |
| Haloperidol | 2 | 0 | 0 |
| None | 8 | 18 | 22 |

SD = standard deviation.
[a]ADHD subjects were significantly younger than schizophrenics ($p < .05$).
[b]IQ of 12 schizophrenics, 18 ADHD, and 22 normal subjects; schizophrenics had a significantly lower mean IQ than ADHD and normal subjects ($p < .0001$).

### *Measurement of Ventricular/Brain Ratio (VBR)*

All subjects were scanned on a GE 1.5 Tesla Signa magnetic resonance scanner. Three-dimensional spoiled grass recalled echo sequence in the steady state (echo-time = 5 msec, recovery time = 24 msec, flip angle = 45°, acquisition matrix = 192 × 256, number of excitations =

1, field of view = 24 $cm^2$) was used to acquire contiguous 1.5 mm thick sagittal and axial slices and 2.0 mm thick coronal slices.

After orientation was standardized, total cerebral volume was derived from an image analysis technique using active surface templates and an energy minimization function. This technique has been validated by comparison to postmortem specimens, and further details are described elsewhere (Snell et al, in press). Lateral ventricular volumes were measured in the coronal plane using an operator-supervised thresholding technique available in an image analysis program developed at the National Institutes of Health (Rasband 1993). Because this process required little subjective judgment, interrater reliability was extremely high (interclass correlation coefficient > .99). VBR was calculated by dividing lateral ventricular volume by total cerebral volume.

### *Eye Movement Procedure*

After being seated 43 cm in front of a video monitor on which a bright square target subtending less than 0.25° of visual angle was displayed against a black background, subjects' heads were stabilized with a bite bar and a headrest. The room was darkened during eye movement tasks. The horizontal eye movements of 39 subjects (10 schizophrenics, 11 ADHD, 18 normals) were recorded using an infrared photoelectric limbus detection eye tracking device [Eye-trac model 210, Applied Sciences Laboratories (ASL), Waltham, MA], which is accurate to within 0.25° of visual angel, and has a time constant of 4 msec and a bandwidth of 250 Hz. The analog output was sampled at 1000 Hz using a 12-bit analog-to-digital converter. Data on this system were collected from the eye on which the most rapid and accurate calibration could be obtained. Eighteen subjects (7 schizophrenics, 7 ADHD subjects, 4 normals) were studied using the Ober2 infrared orbital scanning system. Because this system uses extremely brief pulses of infrared light (pulse rate 600 Hz), and collects data over a few microseconds, it has a time constant of well under 1 msec and a bandwidth of over 1000 Hz.

### *Eye Movement Task*

For the present study, all subjects performed a 60-sec smooth pursuit task at least once. This task began with a series of five consecutive fixation points, each separated from the preceding fixation point by 7.5°, for calibration, after which the target moved horizontally back and forth over 30° for 5 cycles with a constant velocity of 11.0°/sec and a 1.4-sec fixation period between ramps (a "trapezoidal" pattern). Prior to the task subjects were urged to keep their eyes on the target and to follow it as closely as possible during the entire task.

### *Eye Movement Analysis*

Data obtained from the ASL and Ober2 systems were analyzed identically, using the same software. Following data collection, superimposed tracings of eye and target movement were displayed on a computer screen. When subjects performed the smooth pursuit task more than once, the record containing the least amount of eye-blink artifact and the greatest proportion of time engaged in smooth pursuit was selected for analysis. Sections of the records during which subjects were not attempting to track the target (i.e., were not looking at the screen) were identified by visual inspection and were excluded from all analyses.

Eye movement data were analyzed with a computerized pattern recognition system that has been described elsewhere (Nickoloff et al 1991; Radant and Hommer 1992). Briefly, raw data consisted of eye position and target position for each millisecond of recorded tracking. Eye movements were divided into segments, which were classified as saccade, smooth pursuit, or artifact. Saccades were identified on the basis of peak velocity (greater than 25°/sec), initial acceleration (greater than 1500°/$sec^2$), and minimum duration (greater than 8 msec). Artifact caused by blinking exhibits a distinct morphology and was removed from the analysis by the pattern recognition software. Segments not meeting velocity or acceleration criteria for saccade or artifact were classified as smooth pursuit or fixation.

### *Smooth Pursuit*

Because the initiation and cessation of smooth pursuit are physiologically different from its maintenance (Morris and Lisberger 1987; Lisberger and Pavelko 1989), the 250 msec at the beginning and end of each ramp were not analyzed. Smooth pursuit gain was calculated by summing the amplitude of all smooth pursuit intervals and dividing this value by the total amplitude traveled by the target during all smooth pursuit intervals. Because amplitude is the product of velocity and time, and time in the numerator and denominator of this equation is identical, this equation is mathematically equivalent to the ratio of eye velocity to target velocity. Root-mean-square error (RMSE) was calculated by squaring the difference between eye position and target position for all intervals of nonartifactual pursuit tracking, and then obtaining the average of the square root of these numbers (Iacono and Lykken 1979). The percentage of total task time that subjects were engaged in tracking the target was obtained by summing

all intervals of nonartifactual pursuit tracking (including both saccades and smooth pursuit), dividing by total length of the task, and multiplying by 100.

### *Saccade Classification*

Saccades in the direction opposite target motion were classified as back-up saccades. Saccades in the direction of target motion that decreased position error were classified as catch-up saccades, while saccades in the direction of target motion that increased position error, had an amplitude of at least 4°, and were followed by at least 250 msec of pursuit with a gain of 0.6 or less were classified as anticipatory saccades. Square wave jerks were defined as paired saccades of approximately the same amplitude (minimum of 0.5°), with an intersaccadic interval of pursuit lasting 100–450 msec with gain of at least 0.6.

All saccade subtypes were classified by the pattern recognition software, with the exception of anticipatory saccades, which were classified by visual inspection by a rater blind to subject diagnosis (LKJ). Saccade frequency was calculated by dividing the number of each saccade subtype occurring while subjects were engaged in tracking the target by the length of time they were engaged in tracking the target.

### *Data Analysis*

Given that within the schizophrenic and ADHD groups, all of the eye tracking variables were normally distributed and, within the normal group, 82% of the variables were normally distributed, data were analyzed using the following parametric tests: two-tailed $t$ tests for independent samples, Pearson's correlation coefficient, analysis of variance (ANOVA), and repeated measures analysis of covariance (ANCOVA), covarying for age. Age was used as the covariate because smooth pursuit of normal children improves with age in a linearly fashion up to age 14 (Ross et al 1993), the possibility that maturation of smooth pursuit may be different (e.g., delayed) in psychiatric populations, and our observation that age was significantly positively correlated with gain and percentage of task time subjects were engaged in tracking the target and negatively correlated with the frequency and amplitude of several saccade subtypes across the groups. In contrast, IQ was significantly correlated with the frequency of only one saccade subtype in one group (back-up saccades in normals). Thus, correcting for group differences in IQ by using IQ as a covariate could not be justified.

Bonferroni post hoc $t$ tests were used to determine whether significant differences existed between groups. Partial correlation coefficients, controlling for age, were calculated between significant eye tracking variables (gain, RMSE, and average angular distance covered per second by anticipatory saccades), total neurologic examination score, and VBR.

## Results

All subjects completed the task. $T$ tests with Bonferroni correction for multiple comparisons revealed no significant differences across eye movement variables between subjects studied with the ASL system and subjects studied using the Ober2 system. Paired $t$ tests using data from 6 subjects (4 normal and 2 schizophrenic) studied on both systems also revealed no significant differences between the two systems across eye movement variables. Thus, data from the two systems were combined.

Given the small number of schizophrenic subjects tested in the two medication conditions, comparison of eye tracking performance across medication conditions was not possible. Thus, for each of the 17 schizophrenics, the eye tracking record yielding the highest average gain was selected for statistical analysis. This criterion lead to the selection of eight records obtained while subjects were medication free, and nine records obtained while subjects were on medication.

The three groups differed significantly in age [ANOVA, $F(2,54) = 3.41$, $p < .05$], with post hoc tests indicating that ADHD subjects were significantly younger than schizophrenic, but not normal, subjects. Normal subjects did not differ in age from schizophrenics. IQ was also found to be significantly different across the three groups [ANOVA, $F(2,49) = 13.54$, $p < .0001$], and post hoc tests indicated that the schizophrenic group had a significantly lower IQ than both ADHD and normal groups, who did not differ from one another.

### *Eye Tracking Performance*

Table 2 displays measures of pursuit tracking in the three groups along with results of repeated measures analysis of covariance, using age as the covariate. The main effect of gain was significant, with the gain of schizophrenics being lower than that of normals. The gain of ADHD subjects did not significantly differ from that of normals or from that of schizophrenics. RMSE was significantly different across the three groups, and post hoc tests revealed that schizophrenics had higher RMSE than subjects with ADHD, who had higher RMSE than normals but lower RMSE than schizophrenics. The main effect of the percentage of total task time that subjects were engaged in tracking the target was also highly significant. Post hoc tests indicated that schizophrenics spent significantly less time tracking the target than both ADHD and normal

Table 2. Pursuit Tracking Performance of Schizophrenic, ADHD, and Normal Subjects

| Measure | Schizophrenic ($N$ = 17) | ADHD ($N$ = 18) | Normal ($N$ = 22) | $F^a$ (df = 2, 53) | $p$ | Post hoc test |
|---|---|---|---|---|---|---|
| Gain | 0.78 (0.13) | 0.84 (0.12) | 0.86 (0.10) | 4.54 | $p < .05$ | S < N = A |
| RMSE (degrees) | 4.73 (1.98) | 2.88 (1.70) | 1.68 (0.89) | 24.67[b] | $p < .0001$ | S > A > N |
| Percent time tracking[c] | 73.5 (19.1) | 90.8 (10.9) | 98.1 (5.5) | 22.12 | $p < .0001$ | S < A = N |
| Mean saccade frequency (per second) | | | | | | |
| Catch-up | 0.86 (0.44) | 0.70 (0.36) | 0.64 (0.26) | 2.45 | ns | |
| Anticipatory | 0.23 (0.21) | 0.10 (0.08) | 0.05 (0.08) | 15.55 | $p < .0001$ | S > A = N |
| Back-up | 0.44 (0.35) | 0.25 (0.20) | 0.17 (0.12) | 7.22 | $p < .01$ | S > A = N |
| Square wave jerks | 0.21 (0.22) | 0.28 (0.28) | 0.27 (0.26) | 0.61 | ns | |
| Frequency-mean saccadic amplitude product[d] (degrees per second) | | | | | | |
| Catch-up | 2.51 (1.75) | 1.69 (1.56) | 1.17 (0.74) | 5.84 | $p < .01$ | S > N = A |
| Anticipatory | 2.28 (2.00) | 0.67 (0.51) | 0.28 (0.48) | 22.73 | $p < .0001$ | S > A = N |
| Back-up | 2.48 (2.28) | 0.62 (0.85) | 0.22 (0.26) | 15.78 | $p < .0001$ | S > A = N |

Standard deviations in parentheses. RMSE = root mean square error; S = schizophrenic; A = ADHD; N = normal; ns = not significant.
[a]Repeated measures ANCOVA, covarying for age, df = 2, 53.
[b]ANCOVA, covarying for age, df = 2, 53.
[c]Percentage of total task time subjects were engaged in tracking the target.
[d]Average distance covered per second by saccade subtype.

subjects, who did not differ from one another on this measure.

Subtypes of saccades were examined both in terms of their frequency and in terms of the frequency-mean saccadic amplitude product, or average angular distance covered per second by each saccade subtype. This latter measure, which reflects the contribution of different saccade subtypes to tracking, was not applied to square wave jerks because the amplitude of these paired, oppositely directed saccades tends to cancel itself out in the computation. Significant main effects of the frequency of anticipatory saccades and back-up saccades were noted, with post hoc tests indicating that the schizophrenic group had higher rates of both anticipatory and back-up saccades than the ADHD and the normal groups, who did not differ from one another. Although schizophrenics also exhibited a higher frequency of catch-up saccades relative to the control groups, this difference did not achieve significance.

Significant main effects of the frequency-mean saccadic amplitude product of catch-up, anticipatory, and back-up saccades were also observed. On average, schizophrenics covered more distance per second with anticipatory and back-up saccades than either ADHD or normals subjects, who did not differ from one another on this measure for any saccade subtype. Although schizophrenics covered more distance per second with catch-up saccades than normals subjects, they did not differ from ADHD subjects.

To examine whether our sample of schizophrenics exhibits a more severe pattern of eye movement abnormalities than that seen in later-onset schizophrenia, $Z$ scores were derived from studies of adult schizophrenic and normal subjects in which means and standard deviations were reported for gain, RMSE, frequency of catch-up and anticipatory saccades, and amplitude of catch-up and anticipatory saccades. Neither of the two adult studies examining percentage of time engaged in tracking the target reported means and standard deviations (Friedman et al 1992b, 1995). $Z$ scores were computed by dividing the difference between schizophrenic and normal means on a given measure by the standard error of the mean difference. $Z$ scores derived from studies of later-onset schizophrenics and from the present study are shown in Table 3.

Differences between averaged $Z$ scores for each eye tracking variable gleaned from the adult studies and $Z$ scores derived from the analogous variables in the present study were evaluated by dividing them by the square root of 2 (the sum of the variances) and comparing the resulting $Z$ score to a standard normal distribution table for two-tailed $p$ values. These resulting $Z$ scores, reflecting the differences between effect sizes observed in childhood-onset and later-onset schizophrenia, and their associated $p$ values, are also displayed in Table 3. The difference in effect size approached significance for the frequency-mean amplitude product of anticipatory saccades ($Z$ = 1.89, $p$ = .06), with the effect size being greater in childhood-onset schizophrenia. Effect sizes for the other eye tracking variables examined did not differ significantly between childhood- and later-onset schizophrenics.

### *Relationship between Eye Tracking, Clinical and Neurologic Measures, and VBR in Schizophrenics*

Correlations performed between BPRS, AIMS, SANS, and SAPS scores and eye tracking variables, which included gain, RMSE, percentage of time engaged in tracking the target, frequency, and frequency-mean saccadic

Table 3. *Z* Scores Comparing Normal and Schizophrenic Subjects across Eye Tracking Variables from Multiple Studies of Later-Onset and Present Study of Childhood-Onset Schizophrenia

| Eye tracking variable | Later-onset schizophrenia (multiple studies) (*Z* scores) | Childhood-onset schizophrenia (present study) (*Z* score) | Difference (*Z* score[a]) | $p^b$ |
|---|---|---|---|---|
| Gain | | | | |
| Range | 1.60–7.25 | — | | |
| Mean | 3.79[c,d,e,f,g,h] | 2.16 | −1.15 | 0.25 |
| RMSE | | | | |
| Range | 2.12–9.41 | — | | |
| Mean | 5.69[f,i,j] | 6.49 | 0.57 | 0.57 |
| Mean anticipatory saccade frequency | | | | |
| Range | 0.00–2.79 | — | | |
| Mean | 1.46[c,d,e,f,g,h] | 3.60 | 1.51 | 0.13 |
| Frequency-mean saccadic amplitude product | | | | |
| Catch-up | | | | |
| Range | −4.00–11.97 | — | | |
| Mean | 2.10[e,g,h,k] | 3.27 | 0.83 | 0.41 |
| Anticipatory | | | | |
| Range | 1.18–2.56 | — | | |
| Mean | 1.87[e,h] | 4.54 | 1.89 | 0.06 |

RMSE = root mean square error.
[a]*Z* score for difference between childhood- and later-onset schizophrenia.
[b]Two-tailed *p* values for difference between childhood- and later-onset schizophrenia.
[c]Radant and Hommer 1992.
[d]Sweeney et al 1992.
[e]Litman et al 1994.
[f]Grove et al 1991.
[g]Clementz and McDowell 1994.
[h]Radant and Hommer unpublished data.
[i]Sweeney et al 1993.
[j]Gooding et al 1994.
[k]Abel et al 1991.

amplitude products of all saccade subtypes, ranged from $r = 0.31$ (SAPS and frequency-mean saccadic amplitude product of backup saccades) to $r = 0.003$ (BPRS and frequency of anticipatory saccades), with no correlation reaching significance. Partial correlations, controlling for age, between eye tracking variables and the number of neurologic signs revealed only a trend toward gain being negatively correlated with the sum of motor signs (tone, strength, reflexes, Babinski's signs, abnormal involuntary movements, coordination, gait; $n = 14$, $r = 0.57$, $p = .05$). Partial correlations between eye tracking variables and VBR ranged between $r = 0.04$ ($n = 15$, with gain) and $r = -0.28$ ($n = 15$, with frequency-mean saccadic amplitude product of anticipatory saccades), and were not significant.

## Discussion

### *Eye Tracking Performance*

Children and adolescents with very early-onset schizophrenia exhibited significantly greater smooth pursuit impairments than either normal children or children with ADHD. The finding of lower gain in schizophrenics relative to normal controls replicates numerous studies of later-onset schizophrenics (Levy et al 1993).

The finding that schizophrenic children spend significantly less total task time engaged in tracking the target than do normal children replicates and extends similar observations in adult schizophrenics (Friedman et al 1992b, 1995; Cegalis and Sweeney 1979), as does the observation of higher RMSE in schizophrenics relative to normals (Clementz et al 1990; Grove et al 1991; Iacono et al 1992; Ross et al 1988; Sweeney et al 1993). Similarly, the higher rate of anticipatory saccades in schizophrenics compared to normals replicates like findings in adult schizophrenics (Friedman et al 1992a; Litman et al 1994; Sweeney et al 1992). The elevated frequency-mean saccadic amplitude product of catch-up and anticipatory saccades also is consistent with observations in the adult literature (Litman et al 1994).

The frequency of back-up saccades is strongly correlated with the frequency of anticipatory saccades in all groups, as back-up saccades are usually preceded by anticipatory saccades and reflect subjects' attempts to

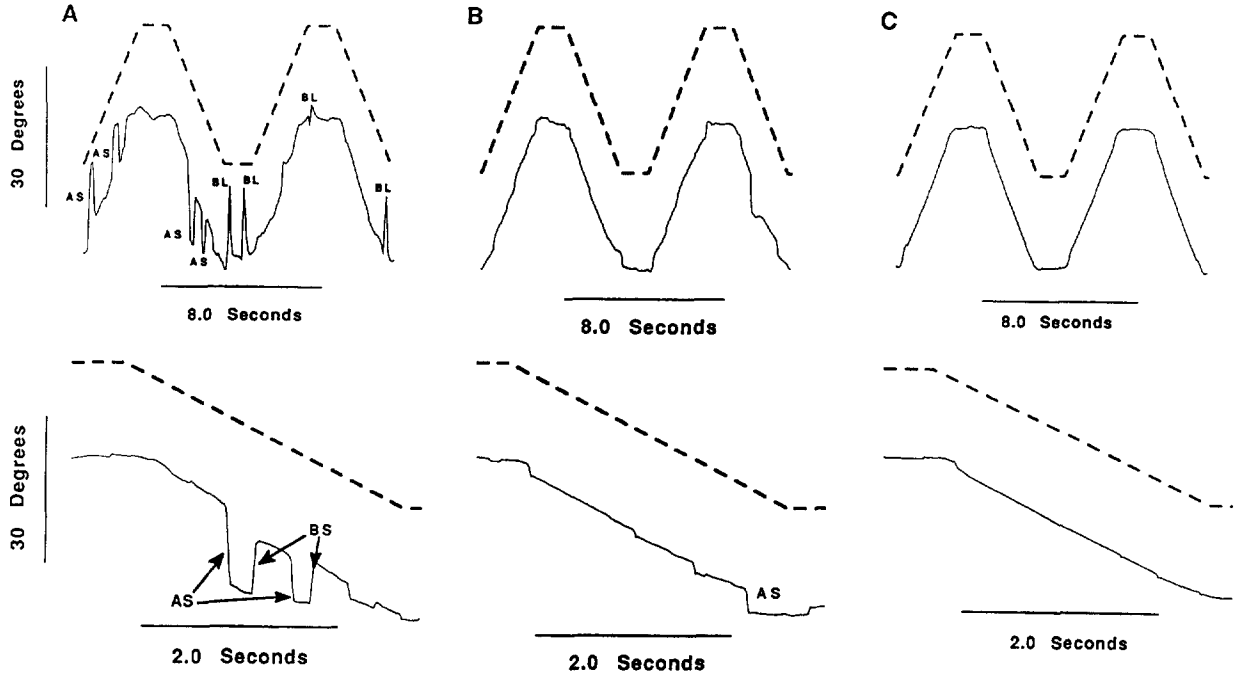


Figure 1. (**A**) Eye tracking record from a 15-year-old medication-free subject with childhood-onset schizophrenia. Top = 16 sec segment. Bottom = enlargement of the first descending ramp. (**B**) Eye tracking record from a 10-year-old subject with ADHD. Top = 16-sec segment. Bottom = enlargement of the first descending ramp. (**C**) Eye tracking record from a 15-year-old normal subject. Top = 16-sec segment. Bottom = enlargement of the first descending ramp. AS = anticipatory saccade; BS = back-up saccade; BL = blink artifact.

refoveate the target. Thus, the increased frequency and frequency-mean saccadic amplitude product of back-up saccades in schizophrenics is likely secondary to the elevated frequency and frequency-mean saccadic amplitude product of anticipatory saccades in this group.

The similarities between the pattern of eye movement abnormalities observed in this sample and those reported in adult schizophrenics indicate continuity between very early- and later-onset forms of this disease. The finding of a trend toward a greater deviation from normals in frequency-mean saccadic amplitude product of anticipatory saccades in childhood-onset schizophrenics relative to that observed in adult schizophrenics is noteworthy. Although this observation must be interpreted with caution, given differences in the conditions under which data were collected in the different studies, it may mean that childhood-onset schizophrenia is associated with greater disinhibition of large, inappropriate, anticipatory saccades relative to that which occurs in adult-onset schizophrenia. Although this difference could represent an enduring greater deficit in childhood-onset schizophrenics relative to later-onset schizophrenics, this difference could also result from a developmental delay in the childhood-onset group that may improve with time. This finding may be of particular interest given recent observations of increased rates of anticipatory saccades in a sample of children at high risk of developing schizophrenia due to their having at least one parent with the disorder (Rosenberg et al 1995).

Phenomenologically, this means that the smooth pursuit of childhood-onset schizophrenics is characterized by low gain with frequent interruptions by large saccades in the direction of target motion, which move their gaze ahead of the target until a back-up saccade occurs. This pattern of smooth pursuit dysfunction cannot be attributed solely to inattention on the part of the schizophrenic group. Attention-enhancing maneuvers improve multiple dimensions of smooth pursuit, including catch-up saccade amplitude, anticipatory saccade frequency, and RMSE, in normals and schizophrenics alike, without abolishing the differences between them (Shagass et al 1976; Sweeney et al 1994a; Schlenker et al 1994). An example of this pattern of smooth pursuit in a schizophrenic patient is shown in Figure 1A. For comparison, sections of typical eye tracking records from ADHD and normal subjects are displayed in Figures 1B and 1C, respectively.

### *Eye Tracking, Clinical Variables, Neurologic Status, and VBR*

The absence of a significant relationship between clinical and eye tracking variables in schizophrenic children is consistent with what investigators have found in adult

schizophrenics (Kelly et al 1990; Sweeney et al 1992). Given the small sample size in this study, however, there may not have been adequate statistical power to detect a relationship among these variables. The lack of even a trend toward significance in the relationship between total AIMS score and any of the eye tracking variables, including frequency and frequency-mean amplitude product of anticipatory saccades, suggests that the disinhibition of anticipatory saccades seen in this sample of schizophrenic children is not related to abnormal involuntary movements, which have been associated with increased frequency of intrusive saccades in adult samples (Oepen et al 1990; Spohn et al 1988).

The trend toward a negative correlation between gain and the sum of motor signs on neurologic examination and the absence of significant correlations between eye tracking variables and VBR in schizophrenic children also are consistent with observations in later onset schizophrenia (Siever and Coursey 1985; Katsanis and Iacono 1991; Siever et al 1986; Katsanis et al 1991; Schlenker et al 1994; Schlenker and Cohen 1995).

### *Specificity of Eye Tracking Abnormalities in Children*

Notably, differences between ADHD and normal subjects' eye tracking performance achieved significance only on the global measure, RMSE. On eye tracking variables where schizophrenics were significantly deficient relative to normals, ADHD subjects performed significantly better than schizophrenics, with the exception of gain and the frequency-mean amplitude product of catch-up saccades. This suggests that, in children, a pattern of abnormalities involving multiple dimensions of smooth pursuit may be specific to schizophrenia. Children with ADHD have been found to fail to inhibit inappropriate saccades during an oculomotor delayed response task (Ross et al 1994), suggesting that more demanding paradigms than the smooth pursuit task used in the present study are required to elicit deficient saccadic inhibition in ADHD.

### *Limitations*

Because schizophrenic children had to fail at least two prior neuroleptic trials to enter this study, greater eye tracking abnormalities in this sample relative to other samples of schizophrenics may reflect this potential selection bias for greater brain abnormalities (Crow 1985) rather than actual differences between childhood-onset and adult-onset schizophrenia.

In the present study, it was not possible to obtain control groups matched to the schizophrenic group in IQ. Although decrements in measured intelligence may be a feature of schizophrenia, the degree to which differences in IQ that were not related to core psychopathology influenced our findings cannot be discerned with these data. Of note, when both age and IQ were used as covariates in the analysis, the significant findings related to gain and to catch-up saccades were lost.

Two recording systems were used to measure eye movements in this study. Although our data suggest that the two systems were comparable, use of two systems may have introduced error into the analysis.

The size of our schizophrenic sample did not permit comparisons across medication conditions. This is a particular concern given evidence that clozapine impairs eye tracking in adults (Friedman et al 1992b; Litman et al 1994). Future research with this population will address the question of differential medication effects. Finally, given evidence that eye tracking abnormalities may be a genetic marker for schizophrenia (Iacono et al 1992; Holzman et al 1988; Grove et al 1992), eye tracking of first-degree relatives of this sample will be examined.

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## References

Abel LA, Friedman L, Jesberger JA, Malki A, Meltzer HY (1991): Quantitative assessment of smooth pursuit gain and catch-up saccades in schizophrenia and affective disorders. *Biol Psychiatry* 29:1063–1072.

Abel LA, Levin S, Holzman PS (1992): Abnormalities of smooth pursuit and saccadic control in schizophrenia and affective disorders. *Vision Res* 32:1009–1014.

Achenbach TM, Edelbrock CS (1983): *Manual for the Child Behavior Checklist and Revised Behavior Profile.* Burlington, VT: University of Vermont.

Alaghband-Rad J, McKenna K, Gordon CT, et al (1995): Childhood-onset schizophrenia: The severity of premorbid course. *J Am Acad Child Adolesc Psychiatry* 34:1273–1283.

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed rev (DSM-III-R). Washington, DC: American Psychiatric Association.

Andreasen NC (1983): *Scale for the Assessment of Negative Symptoms* (SANS). Iowa City, IA: The University of Iowa.

Andreasen NC (1984): *Scale for the Assessment of Positive Symptoms* (SAPS). Iowa City, IA: The University of Iowa.

Bartfai A, Levander SE, Nyback H, Berggren B, Schalling D (1985): Smooth pursuit eye tracking, neuropsychological test

performance, and computed tomography in schizophrenia. *Psychiatry Res* 15:49–62.

Cegalis JA, Sweeney JA (1979): Eye movements in schizophrenia: A quantitative analysis. *Biol Psychiatry* 14:13–26.

Cegalis JA, Hafez H, Wong PS (1983): What is deviant about deviant smooth pursuit eye movements in schizophrenia? *Psychiatry Res* 10:47–58.

Ciuffreda KJ, Alpert M, Blackstone T, Fudge R, Thaler J (1994): Pursuit eye movements in chronic schizophrenics: Relationship between increased saccades and negative symptoms. *Ophthalmic Physiol Opt* 14:79–81.

Clementz BA, McDowell JE (1994): Smooth pursuit in schizophrenia: Abnormalities of open- and closed-loop responses. *Psychophysiology* 31:79–86.

Clementz BA, Sweeney JA (1990): Is eye movement dysfunction a biological marker for schizophrenia? A methodological review. *Psychol Bull* 108:77–92.

Clementz BA, Sweeney JA, Hirt M, Haas G (1990): Pursuit gain and saccadic intrusions in first-degree relatives of probands with schizophrenia. *J Abnorm Psychol* 99:327–335.

Crow TJ (1985): The two-syndrome concept: Origins and current status. *Schizophr Bull* 11:471–486.

Diefendorf AR, Dodge R (1908): An experimental study of the ocular reactions of the insane from photographic records. *Brain* 31:451–489.

Elia J, Borcherding BG, Rapoport JL, Keysor CS (1991): Methylphenidate and dextroamphetamine treatments of hyperactivity: Are there true nonresponders? *Psychiatry Res* 36:141–155.

Frazier JA, Gordon CT, McKenna K, Lenane MC, Jih D, Rapoport JL (1994): An open trial of clozapine in 11 adolescents with childhood-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 33:658–663.

Friedman L, Abel LA, Jesberger JA, Malki A, Meltzer HY (1992a): Saccadic intrusions into smooth pursuit in patients with schizophrenia or affective disorder and normal controls. *Biol Psychiatry* 31:1110–1118.

Friedman L, Jesberger JA, Meltzer HY (1992b): Effect of typical antipsychotic medication and clozapine on smooth pursuit performance in patients with schizophrenia. *Psychiatry Res* 41:25–36.

Friedman L, Schulz SC, Jesberger JA (1993): Smooth pursuit eye movement performance in adolescent-onset psychosis. *Schizophr Res* 9:157.

Friedman L, Jesberger JA, Siever LJ, Thompson P, Mohs R, Meltzer HY (1995): Smooth pursuit performance in patients with affective disorders or schizophrenia and normal controls: Analysis with specific oculomotor measures, RMS error and qualitative ratings. *Psychol Med* 25:387–403.

Gooding DC, Iacono WG, Beiser M (1994): Temporal stability of smooth-pursuit eye tracking in first-episode psychosis. *Psychophysiology* 31:62–67.

Gordon CT, Frazier JA, McKenna K, et al (1994): Childhood-onset schizophrenia: An NIMH study in progress. *Schizophr Bull* 20:697–712.

Goyette CH, Conners CK, Ulrich RF (1978): Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 6:221–236.

Grove WM, Lebow BS, Clementz BA, Cerri A, Medus C, Iacono WG (1991): Familial prevalence and coaggregation of schizotypy indicators: A multitrait family study. *J Abnorm Psychol* 100:115–121.

Grove WM, Clementz BA, Iacono WG, Katsanis J (1992): Smooth pursuit ocular motor dysfunction in schizophrenia: Evidence for a major gene. *Am J Psychiatry* 149:1362–1368.

Herjanic B, Campbell W (1977): Differentiating psychiatrically disturbed children on the basis of a structured interview. *J Abnorm Child Psychol* 5:127–134.

Holzman PS, Kringlen E, Matthysse S, et al (1988): A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. *Arch Gen Psychiatry* 45:641–647.

Iacono WG, Lykken DT (1979): Electro-oculographic recording and scoring of smooth pursuit and saccadic eye tracking: A parametric study using monozygotic twins. *Psychophysiology* 16:94–107.

Iacono WG, Moreau M, Beiser M, Fleming JAE, Lin T (1992): Smooth-pursuit eye tracking in first-episode psychotic patients and their relatives. *J Abnorm Psychol* 101:104–116.

Katsanis J, Iacono WG (1991): Clinical, neuropsychological, and brain structural correlates of smooth-pursuit eye tracking performance in chronic schizophrenia. *J Abnorm Psychol* 100:526–534.

Katsanis J, Iacono WG, Beiser M (1991): Relationship of lateral ventricular size to psychophysiological measures and short-term outcome. *Psychiatry Res* 37:115–129.

Kelly P, Rennie C, Gordon E, Anderson J, Howson A, Meares R (1990): Smooth pursuit eye tracking dysfunction and negative symptoms in schizophrenia. *Psychiatry Res* 34:89–97.

Levin S, Luebke A, Zee DS, Hain TC, Robinson DA, Holzman PS (1988): Smooth pursuit eye movements in schizophrenics: Quantitative measurements with the search-coil technique. *J Psychiatr Res* 22:195–206.

Levy DL, Lipton RB, Holzman PS, Davis JM (1983): Eye tracking dysfunction unrelated to clinical state and treatment with haloperidol. *Biol Psychiatry* 18:813–819.

Levy DL, Bogerts B, Degreef G, et al (1992): Normal eye tracking is associated with abnormal morphology of medial temporal lobe structures in schizophrenia. *Schizophr Res* 8:1–10.

Levy DL, Holzman PS, Matthysse S, Mendell NR (1993): Eye tracking dysfunction and schizophrenia: A critical perspective. *Schizophr Bull* 19:461–536.

Lisberger SG, Pavelko TA (1989): Topographic and directional organization of visual motion inputs for initiation of horizontal and vertical smooth pursuit eye movements in monkeys. *J Neurophysiol* 61:173–185.

Litman RE, Hommer DW, Clem T, Rapaport MH, Pato CN, Pickar D (1989): Smooth pursuit eye movements in schizophrenia: Effects of neuroleptic treatment and caffeine. *Psychopharmacol Bull* 15:473–478.

Litman RE, Hommer DW, Radant A, Clem T, Pickar D (1994): Quantitative effects of typical and atypical neuroleptics on smooth pursuit eye tracking in schizophrenia. *Schizophr Res* 12:107–120.

Morris EJ, Lisberger SG (1987): Different responses to small visual errors during initiation and maintenance of smooth-pursuit eye movements in monkeys. *J Neurophysiol* 58:1351–1369.

Moser A, Kompf D, Arolt V, Resch T (1990): Quantitative analysis of eye movements in schizophrenia. *Neuro-ophthalmology* 10:73–80.

Nickoloff SE, Radant AD, Reichler R, Hommer DW (1991): Smooth pursuit and saccadic eye movements and neurological soft signs in obsessive-compulsive disorder. *Psychiatry Res* 38:173–185.

Oepen G, Thoden U, Warmke C (1990): Association of tardive dyskinesia with increased frequency of eye movement disturbances in chronic schizophrenic patients. *Eur Arch Psychiatr Neurol Sci* 239:241–245.

Orvaschell H, Tabrizi MA, Chambers W (1980): *Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version* (Kiddie-SADS-E), 3rd ed. New York: New York State Psychiatric Institute and Yale University School of Medicine.

Overall JE, Gorham DR (1962): The brief psychiatric rating scale. *Psychol Rep* 10:799–812.

Radant AD, Hommer DW (1992): A quantitative analysis of saccades and smooth pursuit during visual pursuit tracking: A comparison of schizophrenics with normals and substance abusing controls. *Schizophr Res* 11:55–61.

Rapoport JL, Connors CK, Reatig N (1985): Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull* 21:713–1111.

Rasband W (1993): *Image 1.6.* Bethesda, MD: National Institutes of Health (Public Domain).

Reich W, Welner Z (1988): *DICA-RC (DSM-III-R Version), Revised Version V-R.* St. Louis, MO: Washington University.

Rosenberg D, Sweeney J, Cornblatt B, Squires-Wheeler E, O'Hearn K, Erlenmeyer-Kimling L (1995): Eye tracking dysfunction in offspring from the New York high-risk project. *Biol Psychiatry*37:624–625.

Ross DE, Ochs AL, Hill MR, Goldberg SC, Pandurangi AK, Winfrey CJ (1988): Erratic eye tracking in schizophrenic patients as revealed by high-resolution techniques. *Biol Psychiatry* 24:675–688.

Ross RG, Radant AD, Hommer DW (1993): A developmental study of smooth pursuit eye movements in normal children from 7 to 15 years of age. *J Am Acad Child Adolesc Psychiatry* 32:783–791.

Ross RG, Hommer D, Breiger D, Varley C, Radant A (1994): Eye movement task related to frontal lobe functioning in children with attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* 33:869–874.

Sattler JM (1992): *Assessment of Children.* San Diego, CA: Jerome M. Sattler, Publisher, Inc.

Schlenker R, Cohen R (1995): Smooth-pursuit eye-movement dysfunction and motor control in schizophrenia: A follow-up study. *Eur Arch Psychiatry Clin Neurosci* 245:125–126.

Schlenker R, Cohen R, Berg P, et al (1994): Smooth-pursuit eye movement dysfunction in schizophrenia: The role of attention and general psychomotor dysfunctions. *Eur Arch Psychiatry Clin Neurosci* 244:153–160.

Shagass C, Roemer RA, Amadeo M (1976): Eye-tracking performance and engagement of attention. *Arch Gen Psychiatry* 33:121–125.

Siever LJ, Coursey RD (1985): Biological markers for schizophrenia and the biological high-risk approach. *J Nerv Ment Dis* 173:4–16.

Siever LJ, van Kammen DP, Linnoila M, Alterman I, Hare T, Murphy DL (1986): Smooth pursuit eye movement disorder and its psychobiologic correlates in unmedicated schizophrenics. *Biol Psychiatry* 21:1167–1174.

Smeraldi E, Gambini O, Bellodi L, et al (1987): Combined measure of smooth pursuit eye movements and ventricle-brain ratio in schizophrenic disorders, *Psychiatry Res* 21: 293–301.

Snell JW, Merickel MB, Ortega JM, Goble JC, Brookeman JR, Kassell NF (in press): Segmentation of the brain from 3D MRI using a hierarchical active surface template. *Pattern Recog.*

Solomon CM, Holzman PS, Levin S, Gale HJ (1987): The association between eye-tracking dysfunctions and thought disorder in psychosis. *Arch Gen Psychiatry* 44:31–35.

Spohn HE, Coyne L, Spray J (1988): The effect of neuroleptics and tardive dyskinesia on smooth pursuit eye movements in chronic schizophrenics. *Arch Gen Psychiatry* 45:833–840.

Sweeney JA, Haas GL, Li S (1992): Neuropsychological and eye movement abnormalities in first-episode and chronic schizophrenia. *Schizophr Bull* 18:283–293.

Sweeney JA, Clementz BA, Escobar MD, Li S, Pauler DK, Haas GL (1993): Mixture analysis of pursuit eye-tracking dysfunction in schizophrenia. *Biol Psychiatry* 34:331–340.

Sweeney JA, Clementz BA, Haas GL, Escobar MD, Drake K, Frances AJ (1994a): Eye tracking dysfunction in schizophrenia: Characterization of component eye movement abnormalities, diagnostic specificity, and the role of attention. *J Abnorm Psychol* 103:222–230.

Sweeney JA, Haas GL, Li S, Weiden PJ (1994b): Selective effects of antipsychotic medications on eyetracking performance in schizophrenia. *Psychiatry Res* 54:185–198.

Wechsler D (1974): *Wechsler Intelligence Scale for Children—Revised.* New York: The Psychological Corporation.

Weinberger DR, Wyatt RJ (1982): Cerebral ventricular size: A biological marker for subtyping chronic schizophrenia. In Usdin E, Hanin E (eds), *Biological Markers in Psychiatry and Neurology,* Oxford: Pergamon, pp 505–512.

Werry JS, Sprague RL, Cohen MN (1975): Conners' Teacher Rating Scale for use in drug studies with children—An empirical study. *J Abnorm Child Psychol* 3:217–229.